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Advances in Computational Drug Design and Natural Therapeutics: Integrating Artificial Intelligence, Molecular Modeling, and Precision Drug Discovery

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Abstract: Natural compounds offer a large array of molecules with promising therapeutic properties, although their discovery is restricted by chemical complexity, rarity, repeated rediscovery, insufficient target identification, and the burden of experimental screening. This narrative review synthesizes peer-reviewed evidence on AI-driven natural-product discovery, computational drug design, molecular structure prediction, multi-omics analysis, ADMET evaluation, and precision medicine, with emphasis on quantitative findings and the relationship between computational prediction and experimental evidence. Published studies confirm the persistent role of natural-product chemistry in drug discovery, with direct natural-product contributions to small-molecule anticancer drugs reported at approximately one-third and broader natural-product-related contributions approaching two-thirds. An AlphaFold-assisted proteo-chemometric model correctly predicted interactions for 73% of unseen targets, although strong explained variance was achieved in a smaller proportion of cases. Multi-omics and AI-based ADMET models also showed promising but variable predictive performance across datasets. Taken together, the evidence supports a closed-loop approach integrating natural-source characterization, AI-based prioritization, molecular modeling, disease matching, ADMET screening, and experimental validation. The major remaining needs are transparent data curation, independent validation, model interpretability, and reproducible experimental confirmation.

Keywords: natural products; artificial intelligence; machine learning; molecular modeling; virtual screening; multi-omics; precision medicine; ADMET; computational drug design; natural therapeutics

Introduction

Natural products have been a significant contributor to the advancement of modern medicines owing to the fact that biological entities possess molecular structures that cannot be easily reproduced via synthetic approaches [1]. Plant, microbial, fungal, marine, and other biological sources provide metabolites with a range of features such as diverse stereochemistry, three-dimensional structures, and arrangement of functional groups [2]. Such features allow one to find molecules that can interact with complicated biological targets. The significance of natural products is proven by evidence gathered

throughout history of drug discovery [3]. Newman and stated that natural products or their analogs comprised 33.5% of small-molecule anticancer drugs between 1981 and 2019 years. When semisynthetic structures, as well as those considerably inspired by natural products, were taken into consideration, the contribution grew up to 64.9% [4]. Thus, almost two-thirds of the total analyzed small-molecule anticancer landscape had some association with natural-product chemistry. Earlier, in another cancer-drug period, the contribution was 53.3% [5].

Nevertheless, this notwithstanding, conventional natural product discovery is inherently difficult. The extract often contains a complicated mix of metabolites, the active compound may be present at a very low concentration, and related molecules may continually be discovered [6]. Fractionation guided by bioassays may involve a lot of effort and time in terms of extraction, purification, structural determination, and biological testing to discover an interesting molecule [7]. Moreover, the mode of action of many natural products cannot be understood using a one-target framework since their biological activity may involve multiple proteins, signal transduction pathways, and metabolic reactions [8]. Artificial intelligence presents an approach that circumvents these difficulties. Machine learning and deep learning can help incorporate chemical structures, biosynthesis information, metabolomics, protein structures, phenotypic information, and molecular signatures of diseases [9]. Thus, artificial intelligence can help shift the discovery process from extensive experimental screening to computational prioritization whereby the user can determine what sources, metabolites, targets, and molecular structures to experiment on [10].

It has been highlighted by recent reviews that the applications of AI are gradually increasing in natural product discovery with respect to mining of genomes and metabolomes, structural analysis, derelict analysis, biological activity prediction, target finding, and de novo design. Nonetheless, the importance of high-quality data set, validation methods, interpretability, and experimentally verification has been highlighted in the current literature. The purpose of the present review is hence to analyze the role of artificial intelligence, molecular modeling, multi-omics, ADMET prediction, and experimental validation in natural product-based drug discovery. Special attention would be paid towards the quantitative data provided in the literature.

Materials and Methods

A narrative literature-review design was used to synthesize peer-reviewed evidence on natural-product drug discovery, artificial intelligence and machine learning, molecular modeling, multi-omics, ADMET prediction, and precision therapeutics [9], [10], [26]. Studies already assembled in the manuscript were examined for their relevance to the review objectives, with particular emphasis on reports providing quantitative performance measures, experimentally supported computational findings, or integrative drug-discovery frameworks. Extracted information included the computational approach, biological or chemical context, reported performance metric, and major limitation. The evidence was then organized into four analytical domains: AI-driven natural-product discovery, molecular modeling and computational drug design, multi-omics and precision therapeutics, and integrated closed-loop discovery frameworks. Because the source manuscript does not document a reproducible database search string, search date, screening flow, or formal risk-of-bias assessment, the work is presented as a structured narrative synthesis rather than a systematic review.

Results

Artificial Intelligence and Natural-Product Discovery

AI is contributing towards the discovery of natural products through systematic identification of sources, metabolites, and molecular targets. Bioprospecting based on computational methods involves use of information such as genomics, chemistry, ecology, and pharmacology for screening reduction [11]. Genomics aids in the identification of biosynthetic gene clusters that are likely to produce valuable products, while the application of metabolomics and AI-powered derelictions aids in the separation of new chemistry from already existing compounds. It is common knowledge that natural products have therapeutic applications. In 1981-2019, natural products and their derivatives made up 33.5% of small molecule cancer drugs, while natural product related structures made up 64.9% as present in Table 1,

following Nagarajan et al. [12]. These applications include the prediction of anticancer, antimicrobial, and anti-inflammatory activities, although problems such as small sample sizes, class imbalance, domain shift, lack of interpretability, and inadequate experimental validation continue to exist [13]. However, quantitative proof shows that there is both potential and limitations of this approach. An AlphaFold-assisted proteo-chemometric model was able to accurately predict interactions in 73% of unseen targets, with explained variance higher than 0.50 in 22% of cases [14]. Natural product scaffold optimization is another application of generative AI.

Table 1. Quantitative Evidence Supporting AI-Driven Natural-Product Discovery

Discovery Component	Quantitative Evidence	Reference
Direct natural-product contribution to anticancer drug discovery	33.5%	Nagarajan et al. [12]; [13]; [14].
Broader natural-product-related contribution	64.9%	
AlphaFold-assisted interaction prediction	73%	
Cases with explained variance >0.50	22%	
AI-based ADMET validation accuracy	≥75%	

Molecular Modeling and Computational Drug Design

The structural basis for moving AI hypotheses to mechanistic predictions is achieved via molecular modeling. Molecular docking is a tool that assesses the ligand-target interaction and possible binding modes, while molecular dynamics analyzes stability and interaction [15]. However, docking scores cannot serve as the measure of the experimental affinity because protein flexibility, solvation, protonation, and scoring contribute to the predictions' inaccuracies. Protein structure prediction is another method that has widened the scope of the computational targets [16]. Oliveira et al. found that 73% of the predicted interactions are correct based on AlphaFold-predicted structures, while explained variance exceeded 50% in 22% of as present in Table 2. In addition, their study illustrated that there were statistical similarities between predicted and experimentally validated structure which is an indication that there is importance in the use of predicted structures even as they focus on the biological validation process [17]. QSAR represents another technique which is complimentary to the ligand based strategy in the sense that the relationship between molecular descriptors and experimentally validated activity is taken into account [18]. AI-based ADMET models have reached up to 75% validation accuracy which indicates the potential of such models in the early screening of candidates. Recent multi-modal studies have shown AUC scores of 98.9% and 91.0% [19].

Table 2. Metrics Supporting Computational Molecular Modeling and Drug Design

Computational Component	Quantitative Evidence	Reference
AlphaFold-assisted interaction prediction	73% correct interaction prediction	[29]; [15] ; [16].
Explained variance in interaction prediction	>50% in 22% of cases	
AI-based ADMET prediction	≥75% validation accuracy	
Multi-modal drug-response prediction	98.9% AUC	
Multi-omics drug-response prediction	91.0% AUC	

Multi-Omics and Precision Natural Therapeutics

Natural products commonly show multitarget and multilayer effects, which makes multi-omics useful for revealing the therapeutic mechanisms of natural products. Genomics, transcriptomics, proteomics, and metabolomics help to reveal different layers of biology, whereas AI helps to combine all of this information and characterize diseases and treatment outcomes [15]. According to published research, multi-omics approaches can provide different levels of predictive performance. For example, Diamond approach showed an AUC of 67% in differential drug response prediction, outperforming random classification [20]. At the same time, in another research, the MOLI approach showed drug-specific AUC from 39% to 75% in Table 3, with more than 70% performance for several drugs and up to 80% for some targeted therapies [21]. It is evident from the data that predictive performance depends significantly on the drug type, dataset, and molecular context [22]. Validation of a deep-learning multi-omics approach provided accuracies of 66.7% to 90.3%. In natural therapies, such an integration allows for a move away from a compound-to-target relationship toward a compound-to-disease state relationship, with potential evaluation based on the modulation of disease-specific pathways and signatures [23]. There are several challenges to this strategy, including cohort heterogeneity, lack of clinical validation, high computational costs, and the need for models that generalize well.

Table 3. Performance of Computational Approaches in Drug Design

Computational Approach	Reported Performance	Reference
AlphaFold-assisted protein–ligand interaction prediction	73% correct prediction	[22]; [23] ; [22].
AlphaFold-assisted interaction model	>50% explained variance in 22% of cases	
AI-based ADMET prediction	≥75% validation accuracy	
Multi-omics drug-response prediction	91.0% AUC	
Multimodal drug-response prediction	98.9% AUC	

Integrated Closed-Loop Framework

The fusion of artificial intelligence, molecular modeling, multi-omics, and ADMET prediction technologies facilitates a closed-loop system for precision natural product drug discovery. First, natural products are profiled in terms of their chemistry, genomics, and metabolomics, to discover new chemicals and biosynthetic capability [24]. AI technology is applied to select promising metabolites, molecular families, biosynthetic pathways, and biological functions. The selected chemicals are subjected to target and function prediction by means of molecular fingerprinting, QSAR, ligand-based machine learning, and protein-ligand modeling [25]. Structural modeling approaches, such as molecular docking and molecular dynamics, are employed to analyze the mode of action and stability of the interaction [26]. One AlphaFold-powered study reported 73% of correct interaction predictions on an independent target set, but only in 22% of cases the predictive performance was strong [27]. The ADMETox models screen for compounds having undesirable pharmacokinetic or toxicological properties and, indeed, all published models possess validation accuracy of at least 75% [28]. At last, the compounds are screened against the disease-relevant multi-omics signatures. The validation phase is carried out via biochemical, cellular and omics-based experiments. If the predictions are successful, additional training data are obtained. However, unsuccessful predictions will indicate model shortcomings, which can be corrected during future iterations.

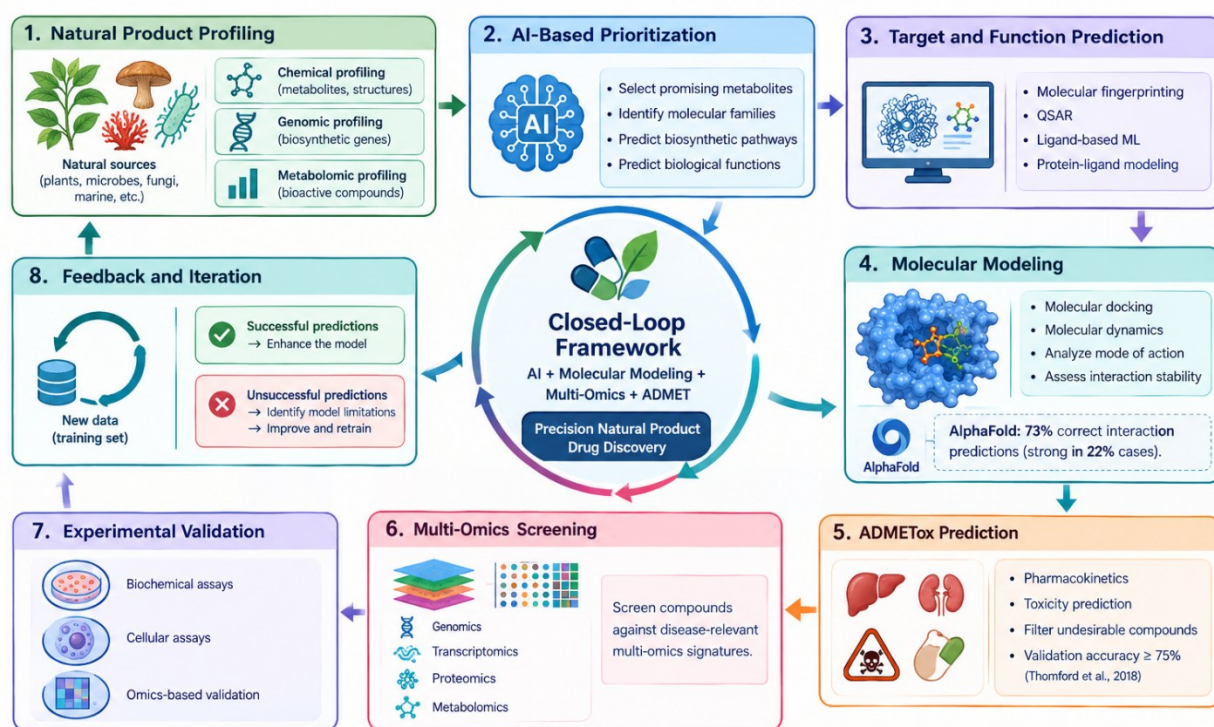


Figure 1. Integrated closed-loop framework for AI driven natural product drug discovery.

Discussion

The reviewed evidence indicates that AI-assisted natural-product discovery is most useful when it functions as a prioritization layer rather than as a substitute for experimental pharmacology. The strong historical contribution of natural-product chemistry to anticancer agents provides a compelling chemical foundation for computational exploration, while recent machine-learning studies show that model performance can be substantial but remains uneven across targets and datasets. The reported 73% correct interaction prediction for an AlphaFold-assisted model, together with stronger explained variance in only a smaller subset of cases, illustrates both the practical value and the current limits of structure-enabled prediction. In this context, model outputs should be interpreted as ranked hypotheses that require biochemical or cellular confirmation rather than as direct evidence of therapeutic efficacy. [3], [12]-[14].

A similar pattern emerges across molecular modeling, ADMET prediction, and multi-omics integration. Docking, molecular dynamics, QSAR, and protein-structure prediction can reduce the experimental search space, but their reliability depends on protein flexibility, solvation, protonation states, scoring functions, and the quality of the underlying training data. Multi-omics approaches extend this framework from isolated compound-target relationships toward disease-state matching; however, the wide range of reported AUC and accuracy values shows that performance is highly dependent on the drug, cohort, molecular context, and validation design. Consequently, comparisons between models should emphasize external validation, reproducibility, and biological relevance rather than isolated high-performance values. [18]-[23], [29].

The principal contribution of the proposed closed-loop framework is therefore its integration of complementary evidence streams. Natural-source profiling, AI-based prioritization, target prediction, molecular modeling, ADMET screening, multi-omics matching, and experimental validation form an iterative sequence in which unsuccessful predictions are informative because they expose model weaknesses and generate new training data. This structure also addresses several limitations identified across the literature, including small or biased datasets, limited interpretability, domain shift, and insufficient independent validation. Future work should report transparent datasets, standardized evaluation metrics, and prospective experimental confirmation so that computational gains translate more reliably into precision natural therapeutics. [24]-[28].

Future Perspectives

Future studies may be oriented towards building better models for natural-product drug discovery using AI. It is crucial to increase the size and improve the curation of datasets that include not only the data from genomics but also data from transcriptomics, proteomics, and metabolomics. Increased usage of explainable AI may allow scientists to understand the way computational models select compounds, targets, and biological pathways. In addition, further improvement of the combination of generative AI, molecular dynamics, docking, and ADMET prediction may contribute to efficient lead optimization. Experiments in different cell and disease models will still be crucial for verification of computational results. Furthermore, standardization and independent validation of computational models may be useful in decreasing model biases and increasing their reproducibility.

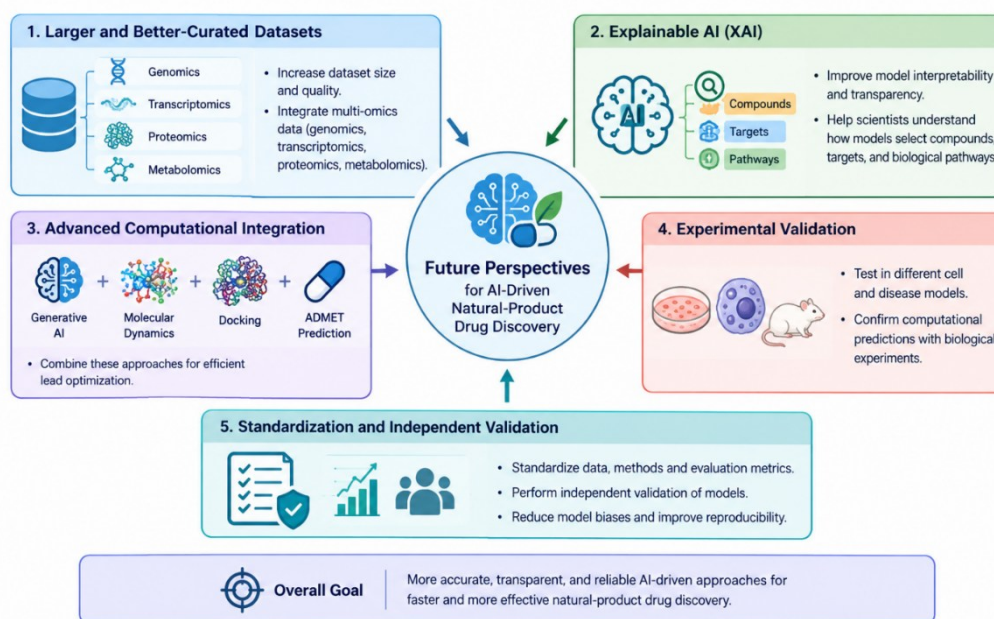


Figure 1. Future perspectives for AI-driven natural-product drug discovery.

Conclusion

Natural products remain valuable sources of pharmacologically diverse chemicals and continue to provide support for drug discovery research. AI is revolutionizing the area by bringing together genome mining, metabolomics, activity prediction, molecular modeling, generative design, and ADMET evaluation into one pipeline. Multi-omics approaches are also helpful for discovering disease-related pathways, therapeutic targets, and treatment responses. At the same time, data quality issues, varying levels of model efficiency, biological complexity, and experimental validation represent notable problems. The suggested closed-loop approach allows overcoming these shortcomings due to the combination of computational prediction with molecular modeling, disease-specific multi-omics, ADMET evaluation, and experimental validation. Feedback from the experiments may be used to further enhance the computational predictions and prioritize candidates. Generally, the combination of natural product chemistry, AI, and experimental science represents a viable strategy for achieving more effective therapeutic discovery.

Author Contributions

S.I. Conceptualization, literature search, data curation, and writing original draft. M.M.H. Literature review, data collection, and writing original draft. P.C. Literature search, data analysis, and writing original draft. J.F. Literature review, visualization, and writing original draft. A.I. Literature search, data curation, and writing review and editing. F.R.N. Literature review, critical analysis, and writing review and editing. E.A.S. Conceptualization, critical analysis, supervision, and writing review and editing. All authors contributed to the development of the manuscript, critically reviewed the manuscript, and approved the final version.

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